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(54) Title: METHOD FOR TREATING OR PREVENTING CHRONIC PROSTATITIS OR CHRONIC PELVIC PAIN SYNDROME

(57) Abstract: The use of a COX-2 selective inhibitor for the treatment or prevention of chronic prostatitis or chronic pelvic pain syndrome is disclosed.

TITLE OF THE INVENTION
METHOD FOR TREATING OR PREVENTING CHRONIC PROSTATITIS OR CHRONIC PELVIC PAIN SYNDROME

BACKGROUND OF THE INVENTION

Chronic prostatitis or chronic pelvic pain syndrome is an extremely prevalent disease in men (Collins MM, et al., "How common is prostatitis? A national survey of physician visits," Journal of Urology, 159:1224-1228 (1998)). Although the epidemiologic evidence is limited, it appears that the prevalence of prostatitis is approximately 2-9% in adult men. It has been suggested that 35-50% of men are affected by prostatitis at some time in life. Approximately 2 million ambulatory patient visits are made annually for prostatitis, accounting for 8% of all visits to urologists and 1% of all visits to primary care physicians. Many men remain symptomatic for much of their lives.

Chronic prostatitis is characterized by evidence of prostatic inflammation and by the presence or absence of white blood cells in prostatic fluid and/or pain associated with the prostate. This syndrome does not exist prior to puberty but has a peak incidence between the ages of 18 and 50. Suggestions as to the origins of these conditions have included a chemical imbalance in the prostate, infection undetected by current microbiological methods and autoimmunity to the prostate gland itself.

Chronic non-bacterial prostatitis and prostatodynia (Chronic Pelvic Pain Syndrome) is characterized by pain and/or discomfort in the genitourinary, pelvic or perineal area and is associated with variable voiding and sexual dysfunction. Chronic nonbacterial prostatitis [Chronic Pelvic Pain Syndrome NIH Category IIIA] is an inflammatory and painful condition of unknown etiology characterized by excessive inflammatory cells in prostatic secretions despite a lack of documented urinary tract infections, and negative bacterial cultures of urine and prostatic

secretions. Prostatodynia [Chronic Pelvic Pain Syndrome NIH Category IIIB] is a painful condition of unknown etiology characterized by a decided lack of inflammatory cells in prostatic secretions, no documented urinary tract infections and negative bacterial cultures in urine and prostatic secretions. Chronic nonbacterial prostatitis is more common than bacterial prostatitis. Symptoms mimic those of chronic bacterial prostatitis. Patients usually show an increase in the number of white blood cells and oval fat bodies in their expressed prostatic secretions. However, they rarely have a history of urinary tract infection, and lower-tract localization cultures fail to reveal a pathogenic organism.

Currently, there are no established treatments for chronic prostatitis. Antibiotics are often prescribed empirically, but with little evidence of efficacy. Alpha blockers are sometimes prescribed, but their efficacy has not been established. Hot sitz baths and anticholinergic drugs can generally be employed to provide some symptomatic relief.

Although the present invention is not limited to a specific mechanism of action, it is noted that COX-2 expression is increased in prostatic tissue involved in chronic prostatitis.

COX-2 selective inhibitors can be administered alone as well as in combination with other active agents. In accordance with the present invention, administration of a COX-2 selective inhibitor reduces both the inflammation and pain that are associated with chronic prostatitis.

SUMMARY OF THE INVENTION

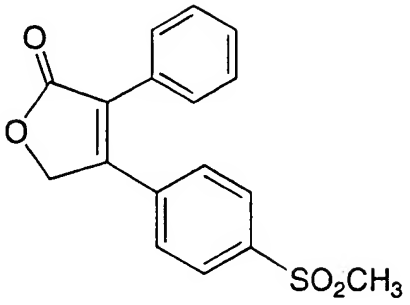
The present invention relates to the use of a COX-2 selective inhibitor for the treatment or prevention of chronic prostatitis or chronic pelvic pain syndrome comprising the administration of a COX-2 selective inhibitor in an amount effective to treat or prevent chronic prostatitis.

DESCRIPTION OF THE INVENTION

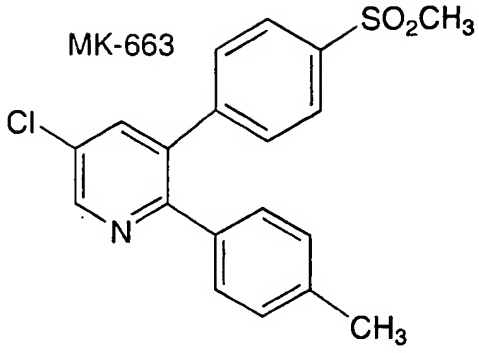
The present invention relates to a method of treating or preventing chronic prostatitis or chronic pelvic pain syndrome in a mammalian patient in need of such treatment or prevention, comprising administering to said patient, and effective amount of a COX-2 selective inhibitor.

As used herein, COX-2 selective inhibitors refers to non-steroidal antiinflammatory drugs that selectively inhibit the enzyme COX-2 in preference to COX-1. Examples include celecoxib, parecoxib, rofecoxib, valdecoxib, meloxicam, flosulide, nimesulide, MK-663, NS 398, DuP 697, SC-58125, SC-58635, and RS 57067. Examples of compounds that are useful in this regard are shown below.

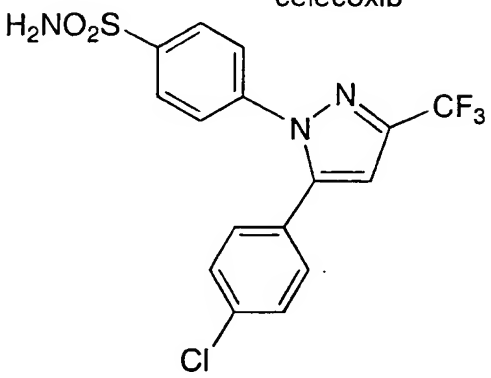
rofecoxib



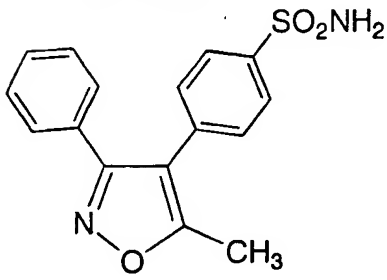
MK-663



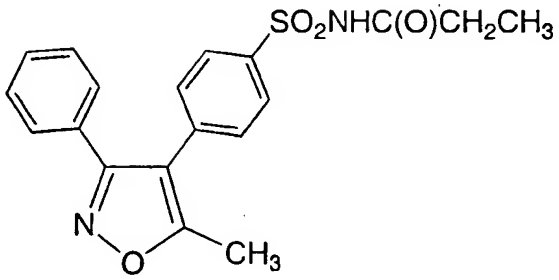
celecoxib



valdecoxib



parecoxib



In a particular embodiment, the present invention provides a method for treating or preventing chronic nonbacterial prostatitis in a mammalian patient comprising the administration of a COX-2 selective inhibitor in an amount effect to treat or prevent chronic nonbacterial prostatitis.

It will be recognized by those skilled in the art from the teachings herein that there are numerous compounds which are useful in combination with COX-2 selective inhibitors for treating or preventing chronic prostatitis, which as used herein includes chronic prostatitis, chronic nonbacterial prostatitis, prostatodynia, congestive prostatitis, epididymitis, post-vasectomy pain and inflammation and/or urethritis. In these combinations, the COX-2 selective inhibitor and the other therapeutic agent may be independently present in reduced dosage amounts such as from about one one-hundredth of the usual adult dose, up to as high as a normal adult dose, which is normally effective when these compounds are used singly. In such combination therapy, the COX-2 selective inhibitor may be administered with the other therapeutic agent (e.g., concurrently, concomitantly, sequentially, or in a unitary formulation) such that their therapeutic effects overlap.

The COX-2 selective inhibitor may be administered in combination with an alpha blocker, especially an alpha-1a blocker, a 5-alpha reductase inhibitor, a prostate specific antigen conjugate, an antibiotic, in particular a carbapenem antibiotic, an anticholinergic agent, a second COX-2 selective inhibitor, a topical urinary analgesic and the like.

For treating or preventing chronic pelvic pain syndrome, including e.g., nonbacterial prostatitis, acute or chronic prostatitis, acute bacterial prostatitis, prostatodynia, congestive prostatitis, epididymitis, post-vasectomy pain and inflammation and/or urethritis in a patient, the COX-2 selective inhibitor may be given in combination with additional compounds such as: an alpha blocker, especially an alpha-1a blocker, such as doxazosin, indoramin, prazosin, tamsulosin or terazosin; a 5-alpha reductase inhibitor, such as dutasteride or finasteride, especially a type 2 5-alpha reductase inhibitor, a dual 5-alpha reductase inhibitor, or combinations of type 1 and type 2 5-alpha reductase inhibitors; a prostate specific antigen

conjugate; an antibiotic, such as, e.g., amikacin, amoxicillin, ampicillin, carbenicillin, cefaclor, cefadroxil, cefamandole, cefazolin, cefoxitin, cephalexin, Rocefin®, cephalothin, cephapirin, cephradine, ciprofloxacin, cotrimoxazole, demeclocycline, doxycycline, erythromycin, gentamicin, kanamycin, methenamine hippurate, methenamine mandelate, minocycline, nalidixic acid, nitrofurantoin, norfloxacin, ofloxacin, sulfamethoxazole, sulfonamides, tetracycline, ticarcillin, tobramycin, trimethoprim or trimethoprim-sulfamethoxazole, in particular a carbapenem antibiotic such as imipenem, meropenem and the like; anticholinergic agents, such as atropine, hyoscyamine, flavoxate, propantheline or oxybutynin; an analgesic, such as acetaminophen; ketorolac tromethamine; a diuretic such as hydrochlorothiazide, spironolactone or spironolactone with hydrochlorothiazide; trovafloxacin; a corticosteroid;; or a topical urinary analgesic, such as phenazopyridine, and salts thereof, and combinations thereof, and the like and combinations thereof.

Typically, the individual daily dosages for these combinations range from about one-fifth of the minimally recommended clinical dosages to the maximum recommended dosage levels.

Naturally, dosages may be adjusted as necessary to permit divided daily dosages and, as noted above, dosages vary depending on the nature and severity of the disease, weight of patient, special diets and other factors. These combinations may be formulated into pharmaceutical compositions as known in the art and as discussed herein.

The dosage of active ingredient in the compositions of this invention may also be varied as necessary such that a suitable dosage form is obtained. The active ingredient may be administered to patients (animals and human) in need of such treatment in dosages that provide optimal pharmaceutical efficacy.

The appropriate dosage level will generally be from about 0.01 μg to about 50 mg per kg patient body weight per day, which may be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 μg to about 25 mg/kg per day; more preferably about 0.5 μg to about 10 mg/kg per day. For example, for treating or preventing chronic nonbacterial prostatitis or prostatodynia or ameliorating the symptoms attendant to chronic nonbacterial prostatitis or prostatodynia in a patient, a suitable dosage level is about 0.1 μg to 25 mg/kg per day, preferably about 0.5 μg to 10 mg/kg per day, and especially about 1 μg to 5 mg/kg per day. In larger mammals, for example humans, a typical indicated dose is about 300 μg to 400 mg orally. A compound may be administered on a regimen of several times per day, for example 1 to 4 times per day, preferably once or twice per day. When using an injectable formulation, a suitable dosage level is about 0.1 μg to 10 mg/kg per day, preferably about 0.5 μg to 5 mg/kg per day, and especially about 1 μg to 1 mg/kg per day. In larger mammals, for example humans, a typical indicated dose is about 100 μg to 100 mg i.v. A compound may be administered on a regimen of several times per day, for example 1 to 4 times per day, preferably once or twice per day, and more preferably once a day.

A particularly preferred subclass of COX-2 selective inhibitors used in the present invention are those compounds which are orally active and long acting. Such compounds can be administered once daily. The use of this subclass of compounds for treating or preventing acute or chronic prostatitis, chronic nonbacterial prostatitis, acute bacterial prostatitis, prostatodynia, congestive prostatitis, epididymitis, post-vasectomy pain and inflammation and/or urethritis, especially chronic nonbacterial prostatitis or prostatodynia, or ameliorating the symptoms attendant to chronic nonbacterial prostatitis, prostatodynia, congestive prostatitis, epididymitis, post-vasectomy pain and inflammation and/or urethritis, especially

chronic nonbacterial prostatitis or prostatodynia, in a patient represents a further aspect of the present invention.

Thus, the present invention provides the use of a COX-2 selective inhibitor in an oral, once-a-day dosage form for treating or preventing acute or chronic prostatitis, chronic nonbacterial prostatitis, acute bacterial prostatitis, prostatodynia, congestive prostatitis, epididymitis, post-vasectomy pain and inflammation and/or urethritis, especally chronic nonbacterial prostatitis or prostatodynia, or ameliorating the symptoms attendant to chronic nonbacterial prostatitis, acute bacterial prostatitis, prostatodynia, congestive prostatitis, epididymitis, post-vasectomy pain and inflammation and/or urethritis, especially chronic nonbacterial prostatitis or prostatodynia, in a patient. The compounds thus exhibit advantageous benefits when compared to conventional methods for treating or preventing chronic nonbacterial prostatitis, prostatodynia, congestive prostatitis, epididymitis, post-vasectomy pain and inflammation and/or urethritis in a patient.

It will be appreciated to those skilled in the art that reference herein to treatment extends to prophylaxis (prevention) as well as the treatment of the noted diseases/disorders and symptoms. Because the specific diagnosis of chronic prostatitis in a particular patient may be difficult, the patient may benefit from the prophylactic administration of the compound in accordance with the present invention.

While the invention has been described herein with reference to certain particular embodiments, those skilled in the art will appreciate that various modifications may be made without departing from the spirit and scope of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A method of treating or preventing chronic prostatitis or chronic pelvic pain syndrome in a mammalian patient in need of such treatment or prevention, comprising administering to said patient of a COX-2 selective inhibitor in an amount that is effective to treat or prevent chronic prostatitis.

2. A method in accordance with Claim 1 wherein the COX-2 selective inhibitor is selected from the group consisting of: celecoxib, parecoxib, rofecoxib, valdecoxib, meloxicam, flosulide, nimesulide, MK-663, NS 398, DuP 697, SC-58125, SC-58635 and RS 57067.

3. A method in accordance with claim 1 wherein the COX-2 selective inhibitor is employed in combination with an agent selected from the group consisting of: alpha-1a blockers, 5-alpha reductase inhibitors, anticholinergic agents, antibiotics, prostate specific antigen conjugates, analgesics and topical urinary analgesics.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/23100

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/18
US CL :514/601

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/601

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	US 6,054,455 A (GUESS et al) 25 April 2000, see claims 1 & 5, and column 32, line 27 to column 33, line 24.	1-3
X,E	US 6,136,831 A (AOTSUKA et al) 24 October 2000, column 8, line 62 to column 9, line 47 and column 11, lines 15-17.	1-3
X	WO 98/46594 A1 (GRELAN PHARMACEUTICAL CO., LTD.) 22 October 1998, see abstract and full text, especially example 1.	1-3
X	Database Medline on STN, US National Library of Medicine (Bethesda, MD USA) No. 94102068, CANALE, et al., 'Treatment of abacterial prostato-vesiculitis with nimesulide', abstract, Drugs, 1993, Suppl. 1, 147-50.	1-2

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 26 OCTOBER 2000	Date of mailing of the international search report 24 NOV 2000
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International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	Database Medline on STN, US National Library of Medicine (Bethesda, MD USA) No.98024769, MELIS et al., 'Controlled clinical study of the efficacy and tolerability of methoxybutropate compared to nimesulide in gynecology', abstract, Minerva Ginecologica, September 1997, 49(9), 409-15.	1-2 ----- 3
X --- Y	Database Embase on STN, No. 1998077308, VENTURINI et al., 'Chronic pelvic pain: Oral contraceptives and non-steroidal anti-inflammatory compounds,' abstract, Cephalalgia, 1997, 17/20 (29-30).	1-2 ----- 3
X	Database medline on STN, US National Library of Medicine (Bethesda, MD USA) No. 93297754, CANALE et al., 'Use of a novel non-steroidal anti-inflammatory drug, nimesulide, in the treatment of abacterial prostatovesiculitis,' abstract, Andrologia, May-June 1993, 25(3) 163-6.	1-2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/23100

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

CAS ONLINE, CAREG, MEDLINE, EMBASE, BIOSIS, TOXLINE, CANCERLIT, PNTTEXT
search terms: prostatitis, chronic pelvic pain, cox-2 selective inhibitors, nimesulide, celecoxib